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Botulinum neurotoxin A for male lower urinary tract symptoms

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Purpose of review

Lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) affects a large number of male patients from 45 years onward, increasing with age. Routine medical treatment is mainly limited to plant extracts, α-blockers, and 5-α-reductase inhibitors. Although all types of drug have a proven efficacy, they often do not sufficiently treat all aspects of LUTS related to BPH. Thus, there is a need for alternatives. Intraprostatic injections with botulinum neurotoxin type A (BoNT/A) seem to be a promising alternative. The purpose of this review is to summarize the most recent findings from basic science and clinical studies in relation to BoNT/A application in BPH-related LUTS, thereby providing insight into the putative mechanism of action, the rationale for the use of BoNT/A in BPH-related LUTS, and the clinical outcomes.

Recent findings

There is some evidence that BoNT/A intraprostatic injections affect both, the static and dynamic component of BPH-related LUTS by reducing the prostate volume and by downregulation of α-1A-adrenoreceptors. Clinical trials demonstrated an easy and minimally invasive intraprostatic application of BoNT/A with a favourable safety profile. Efficacy seems to be good with significant improvements for several months in symptoms, urinary flow rate and reduction in postvoid residual, prostate volume, and also prostate-specific antigen in some studies.

Summary

BoNT/A seems to be a promising alternative in the treatment of BPH-related LUTS with a good tolerance and safety profile. However, the level of evidence is still low and further randomized controlled studies are mandatory.

Keywords

benign prostatic hyperplasia, botulinum neurotoxin A, international prostate symptom score, intraprostatic injection, lower urinary tract symptoms

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Introduction

Botulinum neurotoxin A (BoNT/A), long been used by neurologists for the treatment of focal spasticity of striated skeletal muscles, has been introduced into the field of urology in 1988 for the treatment of Detrusor-Sphincter-Dyssynergia [1]. In 2000, the first BoNT/A application in the smooth detrusor muscle in patients with neurogenic detrusor overactivity was described [2], followed in 2003 by the first results on the injection of BoNT/A into the prostate gland for the treatment of benign prostate hyperplasia (BPH) [3].

BoNT/A is a 150-kDa molecule, consisting of a heavy and a light chain. The known mechanism of action on striated skeletal muscles is the inhibition of acetylcholine release at motoric axon terminals [4,5••]. Thus, it causes a flaccid muscle paralysis, which is however of limited duration (months) due to resprouting of the axon terminals. Therefore, regular reinjection becomes necessary [4].

Basic research on the mechanism of action of BoNT/A in the human and animal urinary bladder rapidly provided evidence of additional BoNT/A effects, including modulation of urothelial and suburothelial receptor expression and neurotransmitter release [6].

Recent research on BoNT/A injections into the prostate revealed further mechanisms of action of BoNT/A and reported promising results for the therapy of lower urinary tract symptoms (LUTS) due to BPH (LUTS/BPH).

This review summarizes and highlights the most recent findings in basic and clinical research on the use of BoNT/A for BPH.

Basic science and proposed mechanism of action

BPH-related LUTS are commonly characterized by a static component related to prostate overgrowth, and by a dynamic component related to an increase in bladder neck/prostatic/urethral smooth muscle cells (SMC) contractile tone. Current pharmacological treatment options target each component separately. Indeed, 5-α-reductase inhibitors (5-ARI) cause prostate tissue shrinkage, thereby targeting the static component, while prostatic/urethral SMC relaxation is achieved by α-1-adrenergic receptor blockers.

Prostatic SMC tone is mainly controlled by sympathetic innervation while prostate size is under both sympathetic and parasympathetic innervation influences [7]. As BoNT/A could act on both sympathetic and parasympathetic innervation [8], it makes sense to investigate the use of BoNT/A to impact both static and dynamic components of BPH/LUTS. However, preclinical studies supporting such effects are scarce.

Effects of botulinum neurotoxin type A on the static component of benign prostatic hyperplasia-related lower urinary tract symptoms

Most of the animal studies have provided evidence that intraprostatic BoNT/A toxin injections induce prostate size reduction in animals [9–11,12•,13••].

Silva *et al.* [13••] performed intraprostatic injections of saline or 10 units (U) Botox in adult male Wistar rats, and reported a significant 30% lower prostate weight 1 week after intraprostatic Botox injections compared to vehicle injections.

Nishiyama *et al.* [12•] also reported a significant lower prostate weight of, respectively, 36 and *22%* at 1 and 4 weeks after intraprostatic injection of a newly purified neurotoxin issued from BoNT/A (when compared to saline injection).

The main concern with these preclinical data is the fact that they were conducted in normal rats. To date, the only published work performed in an experimental model of BPH in dogs does not report any significant effect of BoNT/A on prostate weight [14]. Nevertheless, these results need to be interpreted cautiously since they were obtained from only two animals in each experimental group.

Therefore, there is a need for more preclinical data to better investigate the effects of intraprostatic BoNT/A on prostate size in an experimental model of BPH.

Key points

- There is a scientific rationale for the effect and use of BoNT/A intraprostatic injections in the treatment of BPH-related LUTS.
- BoNT/A intraprostatic injections probably deploys its effect on BPH-related LUTS by reduction of prostate volume and number of α-adrenoceptors.
- Reduction in prostate volume seems to be caused by apoptosis and glandular atrophy (demonstrated in animals only).
- Application technique is simple and safe and the clinical results seem promising with significant reduction in symptoms, urine flow, and postvoid residual.
- Level of evidence is still low in basic science and clinical studies, making further research and randomized controlled trials mandatory.

Mechanisms of action of botulinum neurotoxin type A on the static component of benign prostatic hyperplasia-related lower urinary tract symptoms

The best characterized mechanism of action of BoNT/A-induced reduction of prostate volume is the promotion of apoptosis that has been described in both humans [15] and animals [9,10,12•,13••,14].

Silva *et al.* [13••] reported that apoptosis rate is clearly enhanced in adult rat prostate 1 week following 10 U intraprostatic Botox injection. Interestingly, this study showed that parasympathetic denervation may not participate to this proapoptotic effect while sympathetic innervation restoration by phenylephrine reduced apoptosis rate by 60%. Prostate atrophy [9,11,12•,14,16] and decreased proliferation rate [9] have also been identified in rat and dog prostates treated with BoNT/A. Indeed, using a purified botulinum neurotoxin A, Nishiyama *et al.* [12•] observed histologically a partial atrophy of the prostate gland 1 week following intraprostatic injection in rats. Such an atrophy characterized by acini dilation and epithelial cells flattening was generalized to all parts of the prostate 4 weeks following injection. However, in human prostate, no sign of prostate atrophy could be identified following intraprostatic BoNT/A injection [15].

It is therefore likely that intraprostatic BoNT/A-induced prostate tissue shrinkage involves the enhancement of apoptosis rate. However, the possible involvement of decreased proliferation rate and/or tissue atrophy in the beneficial effects of intraprostatic BoNT/A still need to be confirmed in human BPH tissue.

Effects of botulinum neurotoxin type A on the dynamic component of benign prostatic hyperplasia-related lower urinary tract symptoms

Lin *et al.* [11] reported the consequences of intraprostatic BoNT/A injections on prostatic/urethral SMC tone. In

dogs, while intraprostatic injection of 100 U Botox did not have any effect, 200 U reduced both in-vitro prostate strips contractile responses to KCl, phenylephrine and electrostimulation, and in-vivo urethral pressor responses to i.v. norepinephrine [11]. It is to be noted that these experiments have been performed in dogs without prostate enlargement and that the effects of intraprostatic BoNT/A on prostatic/urethral SMC reactivity in an experimental model of BPH has not been reported to date.

Mechanisms of action of botulinum neurotoxin type A on the dynamic component of benign prostatic hyperplasia-related lower urinary tract symptoms

It has been reported that intraprostatic Botox downregulates the expression of α-1A-adrenoreceptor within rat prostate [9]. Since an overall nine-fold increase in α-1A-adrenoreceptor has been observed in BPH compared with normal prostate [17], and α-1-adrenoreceptors antagonists are successfully used to relieve prostatic/urethral obstruction associated with increased SMC contractile tone in BPH, the downregulation of prostatic α-1A-adrenoreceptors expression following intraprostatic BoNT/A injection [9] represents a strong rationale for using such a treatment for symptomatic BPH. This is further supported by Lin *et al.* [11] who demonstrated that, in dogs, intraprostatic 200 U Botox injection reduced the contractile activity of the prostate when observed 1 month after injection. In this study, it was suggested that two mechanisms could be responsible for such an effect: an impaired release of norepinephrine from adrenergic nerves and an impaired contractile machinery of stromal SMC. Prostate SMC vacuolization was observed and constitute a plausible explanation for the in-vitro decreased contractile response of prostate tissue to KCl. However, it is still needed to determine whether this effect lasts over time or constitutes an irreversible cellular toxic effect. Interestingly, it has also been demonstrated that the cleavage of SNAP-25 (a component of the SNARE complex) by BoNT/A light chain increased outwards potassium currents channels in oesophageal SMC [18]. This effect would tend to hyperpolarize the membrane and thereby decrease smooth muscle tone, since potassium channels constitute an important component of SMC contractile machinery. Studies are however needed to identify such an effect in prostate SMC.

Findings from clinical studies: from technique to indications

In patients, intraprostatic BoNT/A injections exert beneficial effects on BPH-related bladder dysfunction that are linked to prostatic urethral obstruction relief [reduction of the International Prostate Symptom Score (IPSS) voiding symptoms component], but also to bladder dysfunction by itself (reduction of IPSS storage symptoms component). Indeed, the decrease in storage symptoms component of IPSS accounts for 20–55% of total IPSS reduction following intraprostatic BoNT/A injection [19,20].

Three formulations of BoNT/A are currently commercially available, namely Botox (Allergan, Irvine, California, USA), Dysport (Ipsen, Paris, France), and Xeomin (Merz, Frankfurt am Main, Germany). They mainly differ in their envelope proteins covering the BoNT/A molecule and in the application dosage. None of them is yet licensed for the treatment of LUTS or BPH. Thus, application of BoNT/A for LUTS/BPH remains off-label use.

Technique and dosage

In most studies a transperineal injection route with transrectal ultrasound guidance has been described (Table 1), but transrectal and transurethral application routes have been also used [21–26,27•]. Usually a 20–22 G needle is used to perform one to two injections per lobe either without or under local or light general anaesthesia. A total of 200 U Botox in different dilutions are most frequently used, although there is no rationale for this, as dose finding studies are still missing.

Efficacy

The most frequently used outcome parameters to evaluate the efficacy of BoNT/A intraprostatic injections on BPH-related LUTS are the IPSS or the American Urological Association Symptom Index (AUA-SI) (Table 2), Quality of Life Index (QoL-I), maximum urinary flow rate (MUFR), prostate volume, postvoid residual volume (PVRV) and serum levels of prostate-specific antigen (PSA) (Table 2).

The first and still only randomized, placebo-controlled trial on the efficacy of BoNT/A for BPH-related LUTS was published by Maria *et al.* in 2003 [3]. This trial investigated 30 50–80-year-old patients with moderate-to-severe BPH symptoms (Table 3). Patients were either injected with 200 U Botox or saline. AUA-SI, MUFR, prostate volume, serum PSA level, and PVRV were evaluated at baseline, 1, 2, 6, and 12 months after injection with unblinding after 2 months [3]. BoNT/A injections demonstrated significant improvements in all study parameters at 1 and 2 months post-treatment (65% improvement in AUA-SI and 51% decrease of serum PSA) (Table 2). In contrast, placebo did not show any differences to baseline, which is remarkable as placebo usually shows some effect that can reach up to 30% in randomized controlled trials using α-blockers for BPH [28,29]. Follow-up at 6 and 12 months demonstrated persistent efficacy up to 12 months in all parameters

Table 1 Injection techniques and protocols of different studies on intraprostatic BoNT/A injections for benign prostatic hyperplasia-related lower urinary tract symptoms

Study	Injection route	Guidance	Needle size	No. of injections	Dose (units)/product/dilution (units/ml)	Anaesthesia	Antibiotic prophylaxis
Maria *et al.* [3]	Transperineal	Transrectal ultrasound	22 G, 9 cm	2 (1 per lobe in 2 ml)	200/Botox/50	None	n/a
Chuang *et al.* [15]	Transperineal	Transrectal ultrasound	21 G, 20 cm	2 (1 per lobe in 2 ml)	100/Botox/25	i.v. sedation with 50 mg propofol	Cafazolin 1 g i.v. perioperative
Kuo [21]	Cystoscopical	Cystoscopical	23 G	10	200/Botox/10	Light i.v. general anaesthesia	7 days posttreatment antibiotic prophylaxis
Chuang *et al.* [22]	Transperineal	Transrectal ultrasound	21 G, 15 or 20 cm	2 for prostate volume <30 ml (1 per lobe in 2 ml), 4 for prostate volume >30 ml (2 per lobe in 2 ml)	100 for prostate volume <30 ml, 200 for prostate volume >30 ml/Botox/25	i.v. sedation for first 20 cases only, none thereafter	n/a
Park *et al.* [20]	Transperineal	Transrectal ultrasound	22 G, 15 cm	2 (1 per lobe)	100 for prostate volume <30 ml, 200 for prostate volume between 30 and 80 ml, 300 for prostate volume >80 ml/Botox/25 for prostate volume <30 ml, 33.3 for prostate volume >30 ml	None	n/a
Silva *et al.* [23]	Transrectal	Transrectal ultrasound	21 G, 20 cm	4 (2 per lobe in 2 ml)	200/Botox/25	None	Ciprofloxacin 500 mg b.i.d. for 7 days posttreatment
Brisinda *et al.* [24]	Transperineal	Transrectal ultrasound	22 G, 9 cm	2 (1 per lobe in 2 ml)	200/Botox/50	None	n/a
Kuo and Liu [25]	Transperineal	Transrectal ultrasound	n.a.	2–3 (1 per lobe + 1 additional in median lobe if applicable)	200–600/Botox/n/a	Local or light i.v. general anaesthesia	Ciproxin 1 g daily for 3 days
Silva *et al.* [26]	Transrectal	Transrectal ultrasound	21 G, 20 cm	4 (2 per lobe in 2 ml)	200/Botox/25	None	Ciprofloxacin 500 mg b.i.d. for 7 days posttreatment
Nikoobakht *et al.* [27•]	Transperineal	Transrectal ultrasound	20 G	2 for prostate volume <30 ml (1 per lobe in 2 ml), 4 for prostate volume >30 ml (2 per lobe in 2 ml)	300 for prostate volume <30 ml, 600 for prostate volume >30 ml/Dysport/75	local	Cefazoline 1 g i.v. pretreatment and ciprofloxacin 500 mg b.i.d. for 7 days posttreatment

b.i.d. (lat. bis in die), twice daily; BPH, benign prostatic hyperplasia; n/a, not available; LUTS, lower urinary tract symptoms.

Table 2 Efficacy results of different studies on intraprostatic BoNT/A injections for benign prostatic hyperplasia-related lower urinary tract symptoms

Study	Time after BoNT/A injection (months)	No. of patients improved/no. of patients treated	IPSS/AUA-SI	MUFR (ml/s)	PVRV (ml)	Prostate volume (ml)	QoL-I	Serum PSA level (ng/ml)
Maria *et al.* [3]	1	11/15	From 23.2 to 10.6 ($P=0.00001$)	From 8.1 to 14.9 ($P=0.00001$)	From 126.3 to 49.6 ($P=0.00001$)	From 52.6 to 23.8 ($P=0.00001$)	n/a	From 3.7 to 2.1 ($P=0.00006$)
	2	13/15	From 23.2 to 8.0 ($P=0.00001$)	From 8.1 to 15.4 ($P=0.00001$)	From 126.3 to 21.0 ($P=0.00001$)	From 52.6 to 16.8 ($P=0.00001$)	n/a	From 3.7 to 1.8 ($P=0.00001$)
	6	17/19	From 23.2 to 9.1	From 8.1 to 14.6	From 126.3 to 24.2	From 52.6 to 21.0	n/a	From 3.7 to 2.1
	12	17/19	From 23.2 to 8.9	From 8.1 to 15.0	From 126.3 to 24.0	From 52.6 to 20.5	n/a	From 3.7 to 2.3
Chuang *et al.* [15]	1	16/16	From 18.8 to 8.9 ($P=0.0001$)	From 7.3 to 11.8 ($P=0.0001$)	From 67.7 to 25.1	From 19.6 to 17.0 ($P=0.0014$)	From 3.8 to 2.1 ($P=0.0001$)	From 0.8 to 0.72
	3	16/16	From 18.8 to 7.9 ($P<0.05$)	From 7.3 to 11.9 ($P<0.05$)	From 67.7 to 27.3	From 19.6 to 16.7 ($P<0.05$)	From 3.8 to 1.9 ($P<0.05$)	n/a
	6	16/16	From 18.8 to 7.4 ($P<0.05$)	From 7.3 to 12.5 ($P<0.05$)	From 67.7 to 26.4	From 19.6 to 16.9 ($P<0.05$)	From 3.8 to 1.8 ($P<0.05$)	n/a
	10	16/16	From 18.8 to 9.0 ($P<0.05$)	From 7.3 to 12.6 ($P<0.05$)	From 67.7 to 26.8	From 19.6 to 16.4 ($P<0.05$)	From 3.8 to 2.1 ($P<0.05$)	n/a
Kuo [21]	3	7/10	n/a	From 7.6 to 9.9 ($P=0.02$)	From 243.0 to 53.9 ($P=0.002$)	From 65.5 to 45.9 ($P=0.001$)	n/a	n/a
	6	10/10	n/a	From 7.6 to 11.6 ($P=0.05$)	From 243.0 to 36.8 (0.005)	From 65.5 to 49.6 ($P=0.009$)	n/a	n/a
Chuang *et al.* [22]	1[a]	31/41	From 18.7 to 9.8 ($P=0.001$); from 19.3 to 9.5 ($P=0.001$)	From 7.9 to 12.0 ($P=0.001$); from 7.0 to 10.3 ($P=0.001$)	From 64.1 to 35.7 ($P=0.3$); from 161.7 to 45.2 ($P=0.02$)	From 21.1 to 18.0 ($P=0.001$); from 54.3 to 46.3 ($P=0.001$)	From 3.9 to 2.1 ($P=0.001$); from 4.1 to 2.0 ($P=0.001$)	n/a
	3[a]	n/a	From 18.7 to 8.1 ($P<0.05$); from 19.3 to 8.3 ($P<0.05$)	From 7.9 to 12.7 ($P<0.05$); from 7.0 to 9.8 ($P<0.05$)	From 64.1 to 24.1 ($P<0.05$); from 161.7 to 37.6 ($P<0.05$)	From 21.1 to 18.0 ($P<0.05$); from 54.3 to 45.0 ($P<0.05$)	From 3.9 to 2.0 ($P<0.05$); from 4.1 to 2.2 ($P<0.05$)	n/a
	6[a]	n/a	From 18.7 to 7.3 ($P<0.05$); from 19.3 to 5.2 ($P<0.05$)	From 7.9 to 12.7 ($P<0.05$); from 7.0 to 11.9 ($P<0.05$)	From 64.1 to 38.5; from 161.7 to 45.5 ($P<0.05$)	From 21.1 to 17.5 ($P<0.05$); from 54.3 to 45.3 ($P<0.05$)	From 3.9 to 1.4 ($P<0.05$); from 4.1 to 1.8 ($P<0.05$)	n/a
	12[a]	n/a	From 18.7 to 9.0 ($P<0.05$); from 19.3 to 8.3 ($P<0.05$)	From 7.9 to 13.4 ($P<0.05$); from 7.0 to 11.1 ($P<0.05$)	From 64.1 to 40.0; from 161.7 to 93.6	From 21.1 to 17.0 ($P<0.05$); from 54.3 to 47.2 ($P<0.05$)	From 3.9 to 1.8 ($P<0.05$); from 4.1 to 2.4 ($P<0.05$)	n/a
Park *et al.* [20]	1[b]	18/26; 21/26	From 24.2 to 18.5 ($P=0.001$); from 24.3 to 17.5 ($P=0.001$)	From 9.1 to 10.1; from 10.2 to 11.4	From 108.1 to 82.2; from 137.4 to 95.5	From 47.9 to 44.1 ($P=0.001$); from 46.6 to 42.4 ($P=0.009$)	From 4.6 to 3.4; from 5.0 to 3.3	n/a
	3	39/52	From 24.3 to 16.9	From 9.6 to 11.1	From 122.7 to 80.7	From 47.2 to 41.0	From 4.8 to 3.2	n/a
	6[c]	21/23	From 24.0 to 14.7	From 7.4 to 9.4	From 108.7 to 59.4	From 47.5 to 40.8	From 4.7 to 3.0	n/a
Silva *et al.* [23]	1	16/21	n/a	From retention to 9.0	From retention to 80.0	From 70.0 to 57.0 ($P=0.006$)	n/a	From 6.0 to 5.8
	3	17/21	n/a	From retention to 10.3	From retention to 92.0	From 70.0 to 47.0 ($P<0.05$)	n/a	From 6.0 to 5.0 ($P=0.04$)
	6[c]	9/10	n/a	From retention to 11.4	From retention to 66	From 59.0 to 50.0 (0.02)	n/a	From 6.5 to 6.3
Brisinda *et al.* [24]	1	41/77	From 24.1 to 12.6 ($P=0.00001$)	From 8.6 to 13.1 ($P=0.01$)	From 92.1 to 80.3 ($P=0.01$)	From 54.1 to 47.2	n/a	From 6.2 to 4.8 ($P=0.03$)
	2	55/77	From 24.1 to 8.7 ($P=0.00001$)	From 8.6 to 16.5 ($P=0.00001$)	From 92.1 to 40.6 ($P=0.002$)	From 54.1 to 30.9 ($P=0.00001$)	n/a	From 6.2 to 3.0 ($P=0.00001$)
	6	n/a/77	From 24.1 to 10.4	From 8.6 to 13.2	From 92.1 to 34.3	From 54.1 to 24.3	n/a	From 6.2 to 3.6
	12	n/a/77	From 24.1 to 14.0	From 8.6 to 11.4	From 92.1 to 64.7	From 54.1 to 32.0	n/a	From 6.2 to 4.1
	18	n/a/77	From 24.1 to 9.2	From 8.6 to 16.0	From 92.1 to 30.0	From 54.1 to 24.2	n/a	From 6.2 to 2.9
	24	n/a/77	From 24.1 to 10.1	From 8.6 to 15.0	From 92.1 to 32.0	From 54.1 to 27.1	n/a	From 6.2 to 2.6
	30	n/a/77	From 24.1 to 11.1	From 8.6 to 14.5	From 92.1 to 27.1	From 54.1 to 26.9	n/a	From 6.2 to 3.1
Kuo and Liu [25]	6[d]	n/a	From 16.5 to 11.1 ($P<0.05$); from 18.2 to 9.2 ($P<0.05$)	From 9.4 to 10.5; from 8.4 to 10.2 ($P<0.05$)	From 65.3 to 85.7; from 92.7 to 102.2	From 83.4 to 81.6; from 89.7 to 79.8 ($P<0.05$)	From 3.57 to 2.93 ($P<0.05$); from 4.11 to 2.22 ($P<0.05$)	From 5.74 to 3.89; from 5.94 to 5.80
	12[d]	n/a	From 16.5 to 9.4 ($P<0.05$); from 18.2 to 8.9 ($P<0.05$)	From 9.4 to 10.7; from 8.4 to 10.7 ($P<0.05$)	From 65.3 to 68.5; from 92.7 to 113.7	From 83.4 to 76.6 ($P<0.05$); from 89.7 to 76.8 ($P<0.05$)	From 3.57 to 2.53; from 4.11 to 2.04	From 5.74 to 4.14; from 5.94 to 3.87
Silva *et al.* [26]	1	11/11	n/a	From retention to 11.3	From retention to 73.0	From 82.2 to 68.7	n/a	From 6.7 to 6.6
	3	11/11	12.3	From 11.3 to 12.0	From 73.0 to 82.0	From 82.2 to 59.1	3.3	From 6.7 to 5.1
	6	11/11	From 12.3 to 10.0	From 11.3 to 12.3	From 73.0 to 55.0	From 82.2 to 49.0	From 3.3 to 2.4	From 6.7 to 5.1
	12	11/11	From 12.3 to 10.8	From 11.3 to 11.4	From 73.0 to 64.0	From 82.2 to 63.8	From 3.3 to 3.0	From 6.7 to 5.4
	18	11/11	From 12.3 to 11.3	From 11.3 to 10.5	From 73.0 to 58.0	From 82.2 to 73.0	From 3.3 to 3.2	From 6.7 to 5.9
Nikoobakht *et al.* [27•]	1[e]	n/a	From 16.2 to 9.9 ($P=0.004$); from 19.7 to 10.2 ($P<0.001$)	From 6.5 to 12.7 ($P=0.005$); from 6.3 to 12.6	From 37.2 to 21.1; from 50.7 to 25.0 ($P<0.001$)		From 3.2 to 2.3; from 3.6 to 2.4 ($P<0.001$)	
	6[e]	n/a	From 16.2 to 9.0 ($P=0.001$); from 19.7 to 7.8 ($P<0.001$)	From 6.5 to 14.2 ($P=0.001$); from 6.3 to 13.6 ($P<0.001$)	From 37.2 to 20.5; From 50.7 to 10.7 ($P<0.001$)	From 27.3 to 21.6 ($P=0.001$); from 46.6 to 28.8 ($P<0.001$)	From 3.2 to 1.8 ($P=0.001$); from 3.6 to 1.9 ($P<0.001$)	From 1.9 to 1.4; From 2.8 to 1.8 ($P=0.036$)
	12[e]	n/a	From 16.2 to 9.1 ($P=0.003$); from 19.7 to 8.4 ($P<0.001$)	From 6.5 to 13.2 ($P=0.002$); from 6.3 to 14.0 ($P<0.001$)	From 37.2 to 16.1; from 50.7 to 16.3 ($P<0.001$)		From 3.2 to 2.0 ($P=0.005$); from 3.6 to 1.9 ($P<0.001$)	

AUA-SI, American Urological Association Symptom Index; BoNT/A, botulinum neurotoxin type A; IPSS, International Prostate Symptom Score; MUFR, maximum urinary flow rate; n/a, not available; PSA, prostate-specific antigen; PVRV, postvoid residual volume; QoL-I, quality of life index. *P* values indicate significance level in comparison to baseline values.

[a] Outcome parameters are indicated for 100 (upper values) and 200 (lower values) units Botox separately.

[b] Outcome parameters are indicated for the BoNT/A group (upper values) and the BoNT/A + α-blockers group (lower values) separately.

[c] The indicated mean baseline values represent only those patients who participated in this follow-up.

[d] Outcome parameters are indicated for the combined medication group (upper values) and the BoNT/A group (lower values) separately.

[e] Outcome parameters are indicated for the group with prostate volume <30 ml (upper values) and the group with prostate volume >30 ml (lower values) separately.

Table 3 General characteristics of different studies on intraprostatic BoNT/A injections for benign prostatic hyperplasia-related lower urinary tract symptoms

Study	No. of included patients	Mean age ± SD (range), years	Patient characteristics/inclusion criteria	Control group or comparison group	LoE
Maria *et al.* [3]	30	68.8 ± 4.4 (50–80)	AUA-SI >8, MUFR <15 ml/s, voiding volume >150 ml, enlarged prostate volume on DRE	Placebo	1b
Chuang *et al.* [15]	16	66.3 ± 2.8 (n.a.)	Prostate volume <30 ml, MUFR <12 ml/s, inadequate response to α-blocker therapy for >1 month	None	3
Kuo [21]	10	75.2 ± 9.7 (48–92)	Acute or chronic urinary retention, severely difficult urination, large PVRV, failure of treatment with finasteride and α-blocker for >1 year, poor surgical candidates	None	3
Chuang *et al.* [22]	41	69.1 ± 7.1 (n.a.)	IPSS of ≥8, MUFR <12 ml/s, inadequate response or failure to tolerate α-blockers and/or 5-ARI. All had a benign DRE and a PSA level of <4 ng/ml, or a PSA level of 4–10 ng/ml but with a biopsy that showed no malignancy	None	3
Park *et al.* [20]	52	66.4 ± 8.3 (45–84)	Urinary obstruction symptoms as determined by the IPSS and an enlarged prostate gland on digital rectal examination. All patients were treated with an α-blocker with or without a 5-ARI at least one month before this study	BoNT/A + α-blockers	3
Silva *et al.* [23]	21	80.0 ± 2.0 (65–92)	High-risk patients not suitable for prostate surgery, history of indwelling catheter for >3 months due to urinary retention refractory to α-blocker. At time of inclusion none of patients was taking 5-ARI or α-blocker	None	3
Brisinda *et al.* [24]	77	67.9 ± 3.6 (n/a)	AUA-SI >8, MUFR <15 ml/s, minimum voided volume >150 ml, enlarged prostate gland on DRE	None	3
Kuo and Liu [25]	60	74.9 ± 8.3 (n/a)	IPSS >8, combined 5-ARI and α-blocker treatment at full doses >12 months with symptom progression (occurrence of acute urinary retention or increased IPSS by >4) or unsatisfactory therapeutic outcome (persistent difficult urination with either MUFR <12 ml/s and/or PVRV >100 ml)	Combined medical treatment (5-ARI + α-blocker)	3
Silva *et al.* [26]	11	81.7 ± 2.6 (61–92)	High-risk patients not suitable for prostate surgery, history of indwelling catheter for >3 months due to urinary retention refractory to α-blocker. At time of inclusion none of patients was taking 5-ARI or α-blocker	None	3
Nikoobakht *et al.* [27•]	72	63.5 ± 8.5 (49–80)	Enlarged prostate volume in DRE, serum PSA <4 ng/ml, IPSS >8, MUFR <12 ml/s, and normal renal function tests. For serum PSA between 4 and 10 ng/ml, free PSA was measured and the patient was included if free PSA was within the normal range (i.e. 0.02–0.5 ng/ml)	None	3

5-ARI, 5-α-reductase inhibitor; AUA-SI, American Urological Association Symptom Index; BPH, benign prostatic hyperplasia; BoNT/A, botulinum neurotoxin type A; DRE, digital rectal examination; IPSS, International Prostate Symptom Score; LoE, level of evidence; LUTS, lower urinary tract symptoms; MUFR, maximum urinary flow rate; n/a, not available; PSA, prostate-specific antigen; PVRV, postvoid residual volume; SD, standard deviation.

(Table 2). This study represents the starting point of human studies.

Similar results in a similar study population were reported by Brisinda *et al.* in 2009 [24] (Table 3). In a prospective open-label study, 77 patients received 200 U Botox. At 1 and 2 months AUA-SI, MUFR, prostate volume, serum PSA level, and PVRV were significantly improved (Table 2). Retreatments with 200 U were possible, if patients reported no improvements. After the first treatment 71% of patients reported significant improvements. The results remained stable up to 30 months [24] (Table 2). However, 43 reinjections were performed during that time.

In 2006, Chuang *et al.* [22] reported on the effect of a prostate size-related BoNT/A dosing (100 U for <30 ml and 200 U for >30 ml) in 41 BPH-patients who failed treatment with 5-ARI and/or α-blocker (Tables 1 and 3). Significant improvements were observed in IPSS, QoL-I, MUFR, and prostate volume up to 12 months with slightly greater changes of parameters in the 200 U group [22] (Table 2). This later observation might be due to the fact that 200 U were used in larger prostates, which provides a larger impact area and a larger margin for improvements. PVRV showed significant improvements only at 3 months in the 100 U group and at 1, 2, and 3 months in the 200 U group [22].

The first results using Dysport on LUTS/BPH were recently reported by Nikoobakht *et al.* [27•] in a prospective open-label study. A population of 72 males was included using similar inclusion criteria as Maria *et al.* (Table 3). Follow up was 12 months with intermediate evaluation at 1 and 6 months. IPSS, Qol-I, PVRV, and MUFR were evaluated at each follow-up visit. Serum PSA, prostate volume, urine analysis, and urine culture were evaluated at 6 months only [27•]. All parameters significantly improved from 1 up to 12 months in the whole study population with a magnitude of effect that is comparable to the one observed by Maria *et al.* (Table 2). Like Chuang *et al.* [22], Nikoobakht *et al.* [27•] treated different prostate sizes with different dosages of BoNT/A (Table 1). Subgroup analysis showed again differences in the outcome analysis in means that BoNT/A was more efficient in patients with larger prostates regarding the reduction in prostate volume, PSA, and PVRV and the increase in MUFR (Table 2) [22,27•].

Special indications

Several studies already investigated the use of BoNT/A for BPH-related LUTS in special indications, like especially small or large prostates, poor surgical candidates, and as add-on treatment to α-blocker and 5-ARI. The findings are summarized below.

Small prostates

In a small population ($n = 16$), Chuang *et al.* [15] reported the efficacy of 100 U Botox as a second-line treatment following α-blocker therapy in patients with small prostate volumes (<30 ml) and a MUFR less than 12 ml/s (Table 3). IPSS, MUFR, prostate volume, and QoL-I were significantly improved from 1 up to 10 months (Table 2). Mean PVRV was markedly reduced but standard deviations were probably too large to reveal any significance.

Poor surgical candidates for benign prostatic hyperplasia surgery

Kuo [21] treated 10 patients with 200 U Botox who had severe obstruction but were poor candidates for surgery due to co-morbidities (Table 3). Results were rated excellent, if spontaneous voiding occurred in patients with urinary retention or if patients had improvements in voiding pressure, MUFR, and PVRV of more than 25% from baseline values. At 6 months, eight of 10 patients had excellent results and two patients showed improvement. Follow-up at 3 and 6 months demonstrated significant improvements in MURF, PVRV, and prostate volume (Table 2).

In a similar population of 21 males (poor surgical candidates with urinary retention and indwelling catheters), Silva *et al.* [23] reported 2008 about the short-term results of intraprostatic injections of 200 U Botox. At 3 months postinjection, 17 of 21 patients were able to voluntarily empty their bladder with a MUFR of 10.3 ml/s and mean PVRV less than 100 ml (Table 2). Prostate volume decreased significantly from 1 up to 6 months [23].

In 2009, Silva *et al.* [26] reported on the long-term results of a small subgroup ($n = 11$) of their initial evaluation [23]. Follow-up was 18 months, and although IPSS, PVRV, prostate volume, QoL-I, and serum PSA seemed to slowly increase after 6 months, prostate volume remained still significantly below baseline values and patients remained on voluntary voiding up to 18 months [26] (Table 2). A total of 200 U BoNT/A seem to be a valuable alternative treatment for patients who are not suitable for surgical because of poor general condition. Especially the fact that indwelling catheters could be omitted after the treatment in most of the patients is of great value for the patient.

Add-on treatment in patients with large prostates

Park *et al.* [20] investigated in 52 patients with LUTS/BPH the effect of BoNT/A alone and in combination with α-blocker for 4 weeks. Both groups showed significant improvements in IPSS and prostate volume after 1 month with sustained effects up to 6 months in those patients who participated in the follow-up (Table 2). MUFR, PVRV, and QoL-I were not improved at any follow-up. The only difference in both groups was demonstrated for IPSS-5 (weak stream) in favour of

the BoNT/A and α-blocker group, which was interpreted as relative reinforcement of the adrenergic influence by the anticholinergic effect of BoNT/A [20].

Kuo and Liu [25] investigated the effect of BoNT/A on BPH-related LUTS in patients with ongoing but not sufficient treatment with α-blockers and 5-ARI combination therapy since more than 12 months (Table 3). Sixty patients were either assigned to receive 200 U add-on intraprostatic Botox injection or continued medical therapy (control group) [25]. Additional injections were allowed after 2 months with increasing doses up to 600 U, if initial treatment results were not satisfactorily [25]. Although BoNT/A treatment could significantly reduce IPSS, Qol-I, and prostate volume and increase MUFR at 6 months, no significant differences versus the control group were observed at 12 months regarding prostate volume, IPSS, QoL-I, MUFR, and PVRV. The only significant difference was observed regarding QoL-I at 6 and 12 months, showing a difference of small amplitude in favour of BoNT/A treatment [25]. In regard to both, the study by Park *et al.* [20] and Kuo and Liu [25], add-on treatment with BoNT/A to α-blocker and/or 5-ARI treatment seems not to result in additional benefits. However, study design, patients number and power of both studies seem not appropriate to finally conclude on an add-on effect of BoNT/A. Future trials should probably include a run-in period and try to determine if previous medical treatment might influence responding rate.

Adverse events

Only very few and generally mild and self-limited adverse events were reported in some studies (Table 4). Adverse events that occurred were gross haematuria, urinary retention and acute prostatitis [15,25,27•]. In some studies postop indwelling catheter for up to 4 weeks were applied routinely [23,26] (Table 4). Whether this is generally necessary remains questionable and requires further investigation.

Although various treatment strategies for BPH may impact sexual dysfunction (ejaculatory and erectile disorders) [30], only one yet unpublished clinical trial has examined the effects of intraprostatic BoNT/A on sexual function and reported a significant improvement of ejaculatory function without any change in erectile function [31••]. Thus, further studies are needed to investigate the effects of intraprostatic BoNT/A on bladder function and to validate its safety on sexual function.

Onset and duration of effect

In summary of the above-mentioned 10 clinical studies [3,15,20–26,27•], mean onset of action seems to be around 3.5 weeks (range 1–6 weeks) after injection. The mean duration seems to be 11.9 months (range 3–30 months). However, none of those studies was designed to evaluate the exact onset and duration of effect on LUTS after intraprostatic BoNT/A injection. In most studies onset and duration was dependent on the follow-up scheme. Some studies even performed early reinjections in patients with insufficient outcome after first injection [24,25], thereby influencing the study outcome and analysis of effect duration. Thus, studies investigating the exact start and duration of effect are lacking. This is important to be able to estimate cost-effectiveness. In relation to this, dose finding studies, investigations on repeated injections, and studies specifically investigating the impact of the treatment on the QoL using adequate QoL-questionnaires are also missing.

Ongoing studies

There are currently three active but not yet recruiting phase II studies registered at ClinicalTrials.gov investigating efficacy and/or safety of BoNT/A intraprostatic injections for the treatment of BPH-related LUTS. One is a randomized dose comparison study and two are randomized placebo-controlled trials. Interestingly, in one study (NCT00284518), the injection route of BoNT/A has been changed from transperineal to transrectal, showing that there is still an ongoing discussion about the best route of application. There is also a phase II randomized active control study investigating intraprostatic BoNT/A injections for chronic prostatitis and/or

Table 4 Adverse events in different studies on intraprostatic BoNT/A injections for benign prostatic hyperplasia-related lower urinary tract symptoms

Study	Adverse events	Catheterization after injection
Maria *et al.* [3]	None	n/a
Chuang *et al.* [15]	Transient and mild dysuria and haematuria in three patients during the first 24 h posttreatment	For 1 week in one patient with indwelling catheter
Kuo [21]	None	Three patients needed CISC for 2 weeks postop
Chuang *et al.* [22]	None	Only in patients with indwelling catheter
Park *et al.* [20]	None	n/a
Silva *et al.* [23]	None	Foley catheter for 1 month in all patients
Brisinda *et al.* 24]	None	n/a
Kuo and Liu [25]	In totally 50 injections, transient acute urinary retention occurred after 3 (6%), gross haematuria after 7 (14%) and acute prostatitis after 1 (2%) injection	n/a
Silva *et al.* [26]	None	Foley catheter for 1 month in all patients
Nikoobakht *et al.* [27•]	Self-limited gross haematuria in three patients (4.2%)	n/a

BPH, benign prostatic hyperplasia; CISC, clean intermittent self-catheterization; LUTS, lower urinary tract symptoms.

chronic pelvic pain syndrome. Last but not least, there is a randomized, placebo-controlled phase II study currently recruiting that investigates the influence of intraprostatic BoNT/A injections on semen quality.

Conclusion

There is a rationale for the use of intraprostatic BoNT/A to impact both static and dynamic components of BPH/LUTS. Further preclinical data are needed to better investigate these effects and the exact mechanisms of action of BoNT/A within the prostate. Clinical studies show very promising results with significant symptom relief in the majority of treated patients. The application technique is easily feasible and seems to have a low-risk profile with only rare or mild adverse events. However, the level of evidence is still very low and in view of that BoNT/A intraprostatic injections are still off-label use, no general recommendation for the BPH population can be given. There is still very little information on exact onset and duration of effect, on the dose–effect relation, on changes in QoL, on comparison to other or placebo treatment, and on adverse events on sexual function and semen quality. The results of ongoing controlled trials have to be awaited to increase the level of recommendation.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 86).

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